Remarks

The claims now present in this application are Claims 3-6, 10, 11, 23-26 and 61-65.

This submission is to support the Request For Continued Examination under 37 C.F.R. 1.114. In this application, Applicant received a Notice of Allowance dated August 27, 2002. In accordance with this Notice, the Issue Fee is due on November 27, 2002. Upon receiving this Notice of Allowance, an investigation was carried out of the prior art and the information and data supporting the Declaration Under 37 C.F.R. 1.32 of Pascal Bailon filed June 3, 2002 [Declaration I], to ensure compliance with Applicant's Duty of Disclosure under 37 C.F.R. 1.56. As a result of this investigation, it came to Applicant's attention that there were certain discrepancies including errors and omissions in this Declaration I. These arose from the fact that the data reported in Tables 1 and 2 originated from different experiments, which Mr. Bailon incorrectly assumed had all been conducted according to the same protocol.

Accompanying this Request is a second Declaration [Declaration II] by Mr. Pascal Bailon demonstrating that these discrepancies arose through inadvertence and without deceptive intent. This Request is also for the purpose of having the Information Disclosure Statement filed September 3, 2002 in this Application (Paper No. 15) considered.

In view of the discrepancies set forth below, Applicant is filing this Request for Continued Examination to withdraw the Declaration I, as well as to withdraw reliance upon this Declaration I as a basis for demonstrating patentability. Even without the Declaration I, Applicant's claimed invention is patentable over the prior art. From a review of the discrepancies listed below, it is apparent that these discrepancies were inadvertent and unintentional and were made without any deceptive intent. These discrepancies set forth in Paragraphs 1-4 below resulted from the information which Mr. Bailon supplied for presentation in the Declaration and the discrepancy of Paragraph 5 resulted from typographical errors. These discrepancies are as follows:

1. The section titled "Testing Procedure" (at page 12) describes the experimental protocol Applicants used in conducting mouse bioassays to evaluate the biological activity of various PEG-EPO conjugates. In Declaration Table 1, columns titled "30K SPA," "40K PEG2," "20K ALD," and "Di 30K SBA" correctly reflect experimental data from representative bioassays conducted according to this protocol.

2. Applicants note, however, that the Declaration Table 1 columns titled "Vehicle," "EPO," "30 SBA" and "30K MAL" reflect data obtained in a separate assay, which was conducted according to a different protocol from the protocol described in the Declaration. The protocol for this separate assay differed in the following respects from the protocol described in the Declaration :

a) The mice were administered a single 400 ng dose of each conjugate instead of a 10 ng dose of conjugate as noted in the legend for Table 1;

b) The mice were administered four 400 ng doses of EPO instead of a single 10 ng dose of EPO as noted in the legend for Table 1;

c) Instead of tail puncture, blood samples were drawn from the retro-orbital plexus;

d) Blood samples were drawn at 0, 48, 96 and 168 hours instead of 0, 72, 96, 120 and 144 hours as indicated in Table 1. In this regard, a notation that the 72, 120 and 144 hour values in the columns titled "Vehicle," "EPO," "30 SBA," and "30K MAL" were interpolated from the data obtained at other time points was inadvertently omitted from Table 1.

3. Columns titled "Vehicle," "EPO," "30 SBA," and "30K MAL" are expressed in terms of millions of reticulocytes per ml of blood. Columns titled "30K SPA," "40K PEG2," "20K ALD," and "Di 30K SBA" are expressed in terms of number of reticulocytes per 30,000 total cells. The data in columns titled "Vehicle," "EPO," "30 SBA," and "30K MAL," while valid and comparable to each other, are therefore not directly comparable to data in the other columns.

4. The "Vehicle" and "EPO" controls reported in Table 1 therefore apply only to columns titled "30 SBA" and "30 K MAL".

5. Finally, there are three typographical errors in Table 1: in the column titled "30K SPA" the value of 660, reported for 144 hours, should instead read 535; in the column titled "Di 30K SBA", the

value of 944, reported for 120 hours, should instead read 791; and "30 SBA" should instead read "30 K SBA".

As explained in Mr. Bailon's accompanying Declaration II, the discrepancies in the information presented in the Bailon Declaration I were inadvertent and unintentional and resulted from the fact that the data reported in Tables 1 and 2 originated from different experiments, which Mr. Bailon incorrectly assumed had all been conducted according to the same protocol.

Applicant emphasizes that none of the discrepancies substantially affect the overall conclusions that the biological activity of EPO conjugates of this invention enhance the growth of red blood cells for long periods of time after administration and that this enhancement depends upon the type of linking agents used between the EPO and the PEG moiety. It is by utilizing the particular conjugate having EPO conjugated to PEG with a specific linking agent in accordance with this invention that a therapeutically valuable conjugate, having new and unexpected properties, is produced.

To demonstrate these new and unexpected therapeutic benefits, Applicant is enclosing an Abstract, as Exhibit A, titled "Advances in anemia management, innovative erythropoietic agents," by Roche scientist Dr. Anton Haselbeck, which was distributed at the 2002 American Society of Nephrology Annual Congress. This abstract summarizes more recent biological and biochemical data relating to Roche's drug candidate, "CERA", corresponding to the claimed conjugate of this invention having a three carbon separation between the amide bond and the PEG moiety. The abstract explains that CERA (Continuous Erythropoiesis Receptor Activator) was selected by screening candidate conjugate molecules for their effect on reticulocyte count in normocythemic mice. In particular, the abstract highlights several distinct biological and biochemical properties possessed by this particular conjugate:

1. In both rodents, and non-rodents, the systemic clearance of CERA was much lower than that of epoetin, resulting in an increased terminal half-life following intravenous injection.

2. The binding of CERA to the erythropoietin receptor has also been assessed and demonstrated that while the association rate of CERA and epoetin were of similar magnitude, the dissociation rate of CERA was six times faster.

3. It is proposed that the unique binding constant of CERA permits attachment to the erythropoietin receptor and stimulation of erythropoiesis, followed by fast dissociation from the receptor. The extended serum half-life allows this process to be repeated, resulting in modulated, continuous stimulation of erythropoiesis.

4. In pre-clinical animal studies, CERA elicited a greater magnitude and duration of response compared with unmodified EPO, demonstrating CERA to be a more potent stimulator of erythropoiesis than epoetin.

5. In healthy human volunteers, the pharmacokinetic properties of CERA were characterized by a long terminal half-life and low clearance, and CERA induced a potent, dose-dependent stimulation of erythropoiesis using both single and multiple dosing.

As seen from this abstract, the EPO conjugate of this invention has new and unexpected therapeutic properties characterized by its long terminal half-life and low clearance which allows this conjugate when administered to maintain its therapeutic EPO activity for long periods of time. It is the specific nature of each of the components of this tri-part conjugate i.e. the particular protein, with a particular linking agent and PEG moiety which produce the new and unexpected beneficial therapeutic properties.

The unexpectedness of the specific combination of the each of the components to produce the new and unexpected therapeutic properties is demonstrated by various prior art references and in particular the Katre et al. patent, U.S. Patent 4,917,888, Exhibit B and the Nishimura patent, U.S. Patent 4,154,316, Exhibit C. Both the Katre and Nishimura patents were submitted with the Amendment filed June 3, 2002. Both patents demonstrate that it is unpredictable whether the tri-part conjugate of a protein, linker and PEG moiety will produce a product that will have therapeutically beneficial properties. In particular, these patents demonstrate that various linking groups are not equivalent in producing therapeutically beneficial PEG/protein conjugates. In this regard, these patents demonstrate that whether a given linking agent will produce a

therapeutically useful conjugate with a protein will vary depending upon the protein and specific PEG used. Therefore, what is important is to provide a conjugate of a particular protein with a particular linking agent and PEG moiety which will have the activity of the specific protein, in this case EPO, while producing new and unexpected therapeutic properties, as compared to EPO, such as long terminal half-life and low clearance. In this manner, the EPO activity of the conjugate is maintained for long periods of time to supply its therapeutic benefit to a patient.

The claims were rejected, in the Final Office Action, under 35 U.S.C. §103(a) as obvious over Kawaguchi et al. in view of Bailon, Hakimi and Elliott. In view of the reasons set forth in the Amendment filed June 3rd 2202 as to its available reference date, it is submitted that the Campfield reference cited in the Information Disclosure Statement filed on June 3 2002 , should be substituted for the Bailon et al. patent.

This rejection is respectfully traversed since none of these references show a conjugate of EPO with polyethylene glycol. In Kawaguchi et al. polyethylene glycol is not used as part of a conjugate but is a separate ingredient used as a stabilizer in a composition with EPO. Elliot discloses EPO itself and not as a conjugate much less a conjugate with PEG. The PEG in Kawaguchi et al is an ingredient in a formulation with EPO and it does not form a conjugate which can be administered as a unitary pharmaceutical. In place of PEG stabilizers, Kawaguchi et al. disclose that various conventional stabilizers can be utilized including bovine serum albumin, and gelatin. In contrast, Applicant provides a chemically bonded conjugate which upon administration retains the immunological properties of the EPO . Moreover due to the conjugation of EPO with PEG, the claimed conjugates have a longer half life and remain active in the system for long periods of time. These improved therapeutic properties as compared to EPO can be seen from Exhibit A. Nothing in the Kawaguchi et al. or Elliott references discloses conjugating EPO with a PEG moiety.

With respect to pegylated EPO molecules, attention is directed to the Wright et al. patent set forth in the Information Disclosure Statement as part of the Amendment

filed on June 3, 2002 . This patent discloses the use of EPO conjugated to a PEG via a hydrazine derivative. The conjugate formed with a hydrazine derivative is different than the claimed EPO PEG amide conjugate of the instant invention. In the hydrazine derivative conjugate, there is no amide linkage.

In addition, Hakimi et al. disclose various linkages between a protein and the PEG moiety. However, none of these linkages are amide linkages. These linkages are either urea or urethane type linkages with functional groups on both sides of a carbonyl or thio - carbonyl group. In fact, even between these functional groups there is no 2 or 3 carbon methylene bridge such as in the claimed conjugates of this invention. The only type of linking group that can be asserted as being that claimed in the instant application is found in the Campfield reference. Campfield discloses an amide linkage that is separated by 2 carbon methylene chain . See Formula IB on page 10 of this reference. However, the protein that is conjugated in the Campfield reference is the OB protein. Nothing in Campfield or for that matter any other reference would suggest substituting the EPO protein for the OB protein in the Campfield conjugate.

All of the claims of the instant application are directed to a tri-part conjugate of a water soluble polyethylene glycol (PEG) and EPO linked by an amide group through a carbon chain of from 2 to 3 atoms. None of these references teach, much less suggest, the claimed tri-part EPO conjugate. The Katre and Nishimura patents of Exhibits B and C demonstrate that that the members in this tripart conjugate are not interchangeable . The Katre and Nishimura patents demonstrate that various linking agents are not equivalent in forming conjugates. In this regard these patents demonstrate that their use in forming a therapeutically useful conjugate is not predictable and varies depending upon the protein and the specific linking agent used. Whether a linking agent with a given protein and a given PEG moiety will produce a therapeutically useful product will depend upon the given linker and the protein with which it is used. Therefore these patents demonstrate that the success of one linking group with a given protein to form a PEG conjugate does not mean that it could be utilized with other proteins much less the specific protein EPO.

Nishimura teaches against using certain types of linkers, disclosing that undesirable properties occur with conjugates that have certain types of linkers between the protein and the PEG molecule. For example the coupling agents used to make linked conjugates can damage the proteins (page 2, lines 20-24, page 3, lines 15-17, 20-23 of Nishimura). It is for this reason that Nishimura decided to dispense with linkers and make a conjugate where the PEG is directly linked to the protein.

Katre also demonstrates that enhancement of the biological activity of proteins for therapeutic administration by conjugation with polyethylene glycol is basically a selective process and depends upon the specific protein and linking agent. As stated in column 3, lines 54-59 of the Katre '888 patent:

> Furthermore, it is not *a priori* possible to predict which selected proteins would be favorably responsive to treatment with polymers due to the vast difference in pharmacokinetics and physical properties of various proteins.

Katre clearly demonstrates that one cannot predict whether beneficial or deleterious properties would be imparted to the biologically active protein through its conjugation to PEG. Katre teaches that favorable properties depend upon the specifics as to the PEG, linker and the protein. Clearly, this is not a teaching of the equivalence of all proteins, PEG, polymers and linkers for this purpose. That materials may be classified as biologically active proteins, water soluble PEG polymers or linkers does not make them equivalent.

Katre specifically states that the invention disclosed in the Katre patent is limited to a specific linker with three Nishimura specific proteins, such as IL-2 and interferon-α. As stated in column 8, lines 49-61 of the Katre patent :

> "According to the process of this invention, the three types of proteins described above which are normally hydrophobic and water insoluble, are rendered soluble in an aqueous carrier medium ... by modifying the protein through conjugation to a specified polymer ... The success of such modifications of these proteins cannot be predicted from early use of polymer modification of water soluble enzymes and hormones." (Emphasis Added)

Certainly, this is not a teaching that the individual elements or parts of the conjugates utilized in Katre are applicable to all hydrophobic, water insoluble polymers but rather only to the three specific types of proteins with the specific types of linking.

None of the cited references disclose the possibility of substituting the PEG linker utilized in Campfield for the linking system in Wright to produce an PEG-EPO amide conjugate, much less the EPO amide conjugate linked via 3 carbon methylene bridges. In fact, none of the references set forth the possibility that the amide linkage of Campfield could be utilized successfully with EPO to produce an EPO conjugate. The OB protein is a totally different protein from EPO, different in properties and structure from EPO. No basis exists or is set forth for holding these proteins equivalent.

To combine references on the basis that one could substitute a material of one reference for a different material disclosed in another reference as a design choice is not sufficient grounds for obviousness rejection without a suggestion in the art to make this substitution and that such substitution would be successful. No such suggestion appears in any of these references. Attention is directed to In re Vaeck, 20 USPQ 2d 1442 (Fed. Cir. 1991) where the claimed invention was directed to a chimeric gene capable of being expressed in cyanobacteria composed of the DNA for such expression and the gene fragment encoding an insecticidal active protein. The CAFC held that a rejection could not be based upon combining a reference disclosing a chimeric gene for cyanobacteria expression which included this cyanobacteria expression DNA fused to another structural encoding gene combined with another reference disclosing the claimed gene fragment encoding the insecticidally active protein. In so holding, the CAFC stated

> Where the claimed subject matter has been rejected as obvious in view of a combination under §103 requires, *inter alia*, consideration of two factors : (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success... Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure. (Emphasis Added)

As seen from this decision, for an obviousness combination rejection, the references must do more than provide a design choice to make obvious the modifications which produce the claimed product. The references must provide both basis for combining these references to obtain the conjugate and for the reasonable expectation that success would be achieved by this combination. No basis exists in the references for making the required substitution. In addition the references do not disclose that by making such substitution, one would achieve a successful result.

In fact, as pointed out hereinabove, the prior art teach against such substitution and it would not be obvious to select a specific linker for linking a given protein such as in this case, EPO to PEG. Unobviousness, based upon new and unexpected results are achieved when this specific linker is used with EPO to form a PEG conjugate.

Berg et al., U.S. Patent 6,340,742 is not a reference against this application. Please note that the captioned application has an effective filing date of July 2, 1999 based upon provisional application 60/142,254 as noted on page 2 of the aforementioned Office Action. On the other hand, the earliest filing date that Berg can claim is July 2, 1999 based upon provisional application 60/142,243. Since the Berg Patent has the same effective filing date as the captioned application, the Berg et al. Patent cannot be utilized as a reference against the instant application.

Even if the Berg patent were a reference, which certainly is not the case, it would not render obvious the claimed conjugates. Comparing the structures of Berg conjugate, with the structures of conjugates of this invention, it is clear that the structure of the

conjugates of the Berg patent in no way resembles the claimed structure. Nothing in the Berg reference suggests forming the conjugates with the claimed amide linkage and linkers. Berg does not disclose the claimed amide linkage. Besides this, the linkers that Berg does discloses in column 2, lines 15-30, are structurally remote from the claimed linking groups of this invention. Clearly there is no structural similarity between the conjugates of this invention and the conjugates of Berg.

With regard to the double patenting over the claims of Bailon et al. as pointed out before, Bailon taken together with all of the other references, before and after even applying its full disclosure still does not render obvious the claimed invention. Bailon utilizes the linking group with the two carbon separation and with OB protein. There is nothing in the prior art which suggests, much less renders obvious, the use of this linking group with EPO. No basis is set forth as to why the use of a certain linking group with OB protein would render obvious the use of this linking group with EPO.

Based upon the foregoing, it is submitted that this Request for Continued Examination under 37 C.F.R. 1.114 should be granted to withdraw reliance upon the Declaration Under 37 C.F.R. 1.32 of Pascal Bailon filed June 3, 2002. Even without this declaration it is clear that all of the claims in this application are patentable over the prior art and this application is in condition for allowance. A prompt Notice of Allowance is respectfully requested.

Correspondence and Fees

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Respectfully submitted.

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Version With Markings to Show Changes Made

61. (Amended) A conjugate comprising an erythropoietin glycoprotein having a free amino group and having the *in vivo* biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells and selected from the group consisting of human erythropoietin and analogs thereof which analogs have sequence of human erythropoietin modified by the addition of from 1 to 6 glycosylation sites or a rearrangement of at least one glycosylation site; said glycoprotein being covalently linked to a poly(ethylene glycol) group[s] of the formula $-CO-(CH_2)_x-(OCH_2CH_2)_m-OR$ by the -CO of said poly(ethylene glycol) group forming an amide bond with said free amino group[s]; wherein R is lower alkyl; x is 2 or 3; m is from about 450 to about 900; and m is chosen so that the molecular weight of the conjugates minus the erythropoietin glycoprotein is from 20 kilodaltons to 100 kilodaltons.

62. (Amended) The conjugate of claim 61 of the formula:

$$P-NHCO-(CH_2)_x-(OCH_2CH_2)_m-OR \qquad (I)$$

wherein m, x and R are as above

and P is the residue of the glycoprotein without the [n] free amino group [(s)] which forms the amide linkage[(s)] [with the poly(ethylene glycol) group(s)].